BNC105 is a Phase II tubulin depolymerisation agent that exerts direct anti-cancer efficacy through the selective destruction of solid tumor microvasculature and direct suppression of tumor cell proliferation. A single i.v. dose of BNC105 causes a very high degree of tumor hypoxia leading to >90% necrosis in rodent tumor models. The therapeutic window of BNC105 has been shown to be superior when compared to similar compounds in its class, highly specific to tumor vasculature with minimal off target activity, proving it to be clinically well tolerated. Complementary studies in models of chronic lymphocytic leukemia have shown that BNC105 also activates NK dependent apoptosis, mediating cancer cell death.

Currently there is a very strong drive to extend the clinical benefit of immunotherapies to a broader patient population where many patients fail to respond. This translates to a strong focus being placed on ‘awakening’ tumors and stimulating the immune system to checkpoint inhibitors in tumors that would otherwise be tolerated and evade the unanswered therapeutic benefit of checkpoint inhibitors. In the absence of an innate and pre-existing tumor immune response, stimulating an initial immune response by altering the immune homeostasis can be the key to making immunotherapy relevant to more patients. The placement of BNC105 in this therapeutic setting is potentially beneficial for sustainable patient response to immunotherapy.

BNC105-induced tumor microvasculature destruction, tumor hypoxia and necrosis led to changes in the tumor microenvironment and the surrounding immune landscape. Recent evidence demonstrates that microtubule-depolymerizing agents not only cause an efflux of immune-presenting tumor antigens via tumor disruption/necrosis but also enhanced maturation of dendritic cells into antigen presenting cells and the release of pro and anti-inflammatory cytokines. This has a net effect of firstly disrupting the status quo of immune dormant tumors and is an opportunity to re-activate anti-tumor immunity. These observations led us to examine key immune clinical biomarkers from BNC105 treated patients and investigate pre-clinically the potential therapeutic benefit of combining BNC105 with the checkpoint inhibitors that target PD-1 or CTLA-4.

The balance between pro-inflammatory and anti-inflammatory signals provided by different immune cell populations is crucial for normal physiology and the suppression of cancer development. By altering this homeostasis an opportunity is provided for the immune system to alter the way it responds. Biomarker analysis on patient samples was conducted from a Phase I BNC105 microtherapy melanoma trial. Biomarker analysis showed that plasma IL-12 subunit p40 significantly increases post-BNC105 administration and remains elevated at Day 3 post dosing. The immune modulatory cytokine IL-12 subunit p40, a key member of the IL-12 cytokine family, has emerged as a potent inducer of antitumor immunity. IL-12 subunit p40 is secreted by activated macrophages that serves as an essential inducer of Th1 cells development. This cytokine has been found to be important for sustaining a sufficient number of memory/effector Th1 cells.

Significant changes were also seen in levels of the immune-modulatory cytokine IL-10. IL-10 mediates stimulation of adaptive immunity to tumors that has been observed clinically. IL-10 increases monocytes which are able to induce the expansion of tumor resident CD8+ T-cells in tumors and enhance their cytotoxic activity.

BNC105 clinically enhances the immune response IL-12 p40 and IL-10

BNC105 is a Phase II potent and highly selective disruptor of tumor microvasculature causing rapid onset of tumor hypoxia and necrosis. Tubulin-depolymerising agents can cause an efflux of tumor antigens being presented to the immune system and can simultaneously aid the maturation of dendritic cells rapidly generating antigen presenting cells. It was shown pre-clinically that tumor IL-12, a key regulatory cytokine, is induced by BNC105 treatment correlating with an influx of complementary immune cells. Additionally CD11b+ cells were significantly reduced after BNC105 treatment, subsets of which are known to repress immune activity. The priming of the immunogenic potential of a tumor may work directly in concert with checkpoint inhibitors. The strong synergy of BNC105 with both anti CTLA-4 and PD-1 was demonstrated in immune competent in vivo models with high tumor growth inhibition observed. This synergy may be due to BNC105 priming the immune system, complementing the action of the checkpoint inhibitors.

Clinically BNC105 has been shown to increase plasma IL-12, a known inducer of tumor CD8+ cells which also enhances their cytotoxic activity via elevated granule release. IL-12 subunit p40, the pro-inflammatory cytokine, show pre-clinically to be a potent and robust inducer of tumor immunity was also significantly increased by BNC105 treatment in clinical patient samples. Rapid shifting the balance of pro-inflammatory and anti-inflammatory signals provides an opportunity for an elevated immune response towards the tumor.

These findings strongly support clinical evaluation of BNC105 in combination with checkpoint inhibitors. BNC105 drives priming of the tumor and immune system may extend the reach of checkpoint inhibitors to leverage a therapeutic benefit to a greater patient population.